A Family with Saethre-Chotzen Syndrome: Case Report

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Abstract

Saethre-Chotzen syndrome (SCS) is a rare genetic disorder inherited in an autosomal dominant pattern, characterized by coronal synostosis, facial asymmetry, syndactyly, ptosis and ear anomalies. Even among affected individuals in the same family, the signs of SCS can vary widely. Most cases of SCS are caused by mutations in the *TWIST1* gene. We present a familial case of Saethre-Chotzen (2 siblings and their mother) diagnosed in Iași Medical Genetics Center, in order to identify the clinical particularities of each member of the family. The cases were confirmed using MS-MLPA which identifies the mutation in the *TWIST1* gene. Mother (51 years old): normal growth, acrocephaly, dysmorphic face, facial asymmetry, syndactyly of the 2nd and 3rd finger, deafness, mild intellectual disability. Daughter (16 years old): growth deficiency, acrocephaly, dysmorphic face, facial asymmetry, left ptosis, small ears, hypermobile joints, partial syndactyly of the 2nd and 3rd finger, deafness, excessive aggressivity, moderate intellectual disability. Son (15 years old): normal growth, acrocephaly, mild dysmorphic features, mild facial asymmetry, bilateral ptosis, syndactyly of the 2nd and 3rd finger, 5th finger clinodactyly, hypermobile joints, deafness, excessive aggressivity, mild intellectual disability. From the mother's family history we discovered that the maternal grandfather, as well as his mother present the same facial features and seem to be affected, but a genetic examination and testing were not possible. In conclusion, we present this family to underline the importance of systematic and multidisciplinary approach for individual and family management.

Keywords: Saethre Chotzen syndrome, craniosynostosis, familial, TWIST1 gene

Introduction

Saethre-Chotzen syndrome (SCS) is a genetic disorder that affects both sexes equally, mainly characterized by coronal synostosis (sometimes other cranial sutures can be involved), facial asymmetry with deviation of the nasal septum and ear anomalies with a characteristic appearance of the ear (prominent crus with a small helix) [1-6]. Individuals with SCS might associate cutaneous syndactyly, most commonly of the 2nd and 3rd fingers or 3rd and 4th toes [7, 8].

Although most patients present normal intellectual development, intellectual disability of mild to moderate degree is usually described at those with large genomic deletions [3, 6, 9].

The inheritance is in an autosomal dominant manner but can come with wide phenotypic variability and incomplete penetrance [9]. The mutant gene that causes SCS is *TWIST1* [1, 3-5,

10]. *TWIST1* is an important transcription factor and part of a signaling pathway involved in early embryogenesis and later in chondroblast and osteoblast differentiation [4, 10, 11].

Mutations of the *TWIST1* gene, located 7p21-p22, are detected in more than half of the affected individuals but translocations, inversions or ring chromosome 7 involving 7p21 have been reported in the literature as well [3, 4, 6, 9, 11, 12]. Many individuals diagnosed with SCS have an affected parent but it is not excluded that a proband with SCS presents a de-novo pathogenic variant. The family history is very important because due to the wide phenotypic variability it might bring difficulties in recognizing the disorder in other family members [6, 13, 14].

We present a Romanian family diagnosed with SCS (2 siblings and their mother) at the Regional Center of Medical Genetics in "St. Mary" Children's Hospital Iasi-Romania.

Clinical reports

The family history indicated that the father was 63 years of age, the mother 33 at conception, with no history of family consanguinity (Fig. 1). The couple has another child with similar craniofacial anomalies and a daughter that died at the age of 12 years old (unknown cause). The familial anamnesis shows that the mother is also diagnosed with deafness (Fig. 2, Fig. 3) from the age of 5 years old and the father smokes and drinks alcohol frequently. A maternal aunt is known with a psychiatric disorder and the maternal grandmother died because of breast cancer.

Further family studies revealed that, to a varying extent, clinical signs of SCS were found in 2 of the other family members (maternal grandfather and maternal great-grandmother) but we couldn't get a detailed clinical investigation (both 2 members of the family are deceased).

Our proband (Fig. 4), age 11 years old, was a normal term baby (1st pregnancy) with a birth-weight of 2350 gr. She was referred to our department for left palpebral ptosis and frontal bossing (Table. 1).

The brother of our proband (Fig. 5), 9 years old at the moment of the examination, was a normal term baby with a birth weight of 2300 g, normal delivery. He was brought at our department for evaluation after a episode of pneumonia, anemic syndrome and a positive family history of SCS (Table. 1).

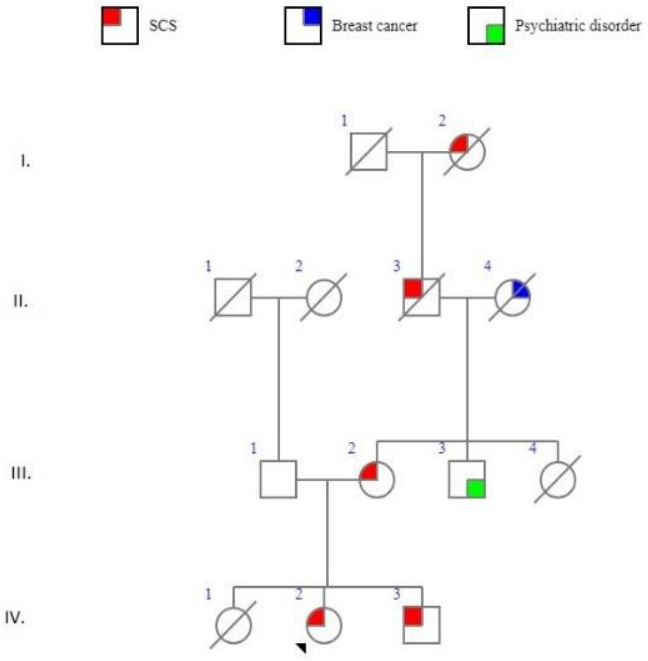


Fig. 1. Pedigree of the family with SCS. The proband is marked with an arrow

Table 1. Clinical features found in all 3 members of the family

Mother	**Son**	**Daughter**
Normal measurements	Normal measurements	Growth deficiency
Acrocephaly	Acrocephaly	Acrocephaly
Mild dysmorphic features	Mild dysmorphic features	Dysmorphic face
Facial asymmetry	Mild facial asymmetry	Facial asymmetry
Absent ptosis	Bilateral ptosis	Left ptosis
Syndactyly of the 2nd and 3rd finger	Syndactyly of the 2nd and 3rd finger	Syndactyly of the 2nd and 3rd finger
Absent hypermobility	Hypermobile joints	Absent hypermobility
Deafness	Deafness	Deafness
Normal behavior	Excessive aggressivity	Excessive aggressivity
Mild intellectual disability	Mild intellectual disability	Moderate intellectual disability
Not investigated	Hands X-ray: bilateral I phalange of the 5th finger "barrel-shaped"; Chronic adenoiditis; Sinus arrhythmia	Hands X-ray: bilateral I phalange of the 5th finger "barrel-shaped"; Nasal septum deviation

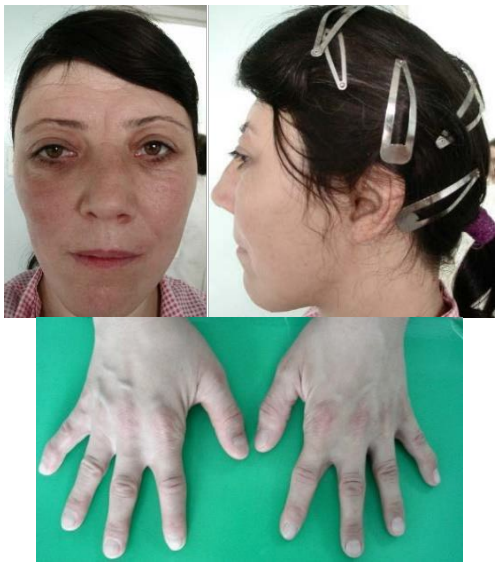
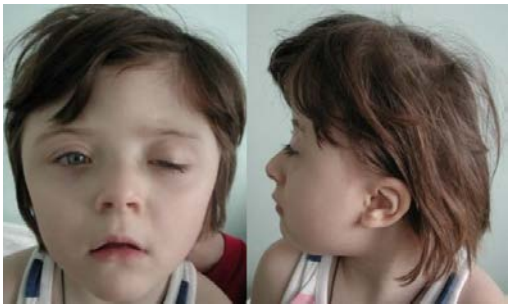


Fig. 2. Facial and hands appearance (mother)

Fig. 3. All 3 members of the family (daughter – left, mother – middle and son – right)



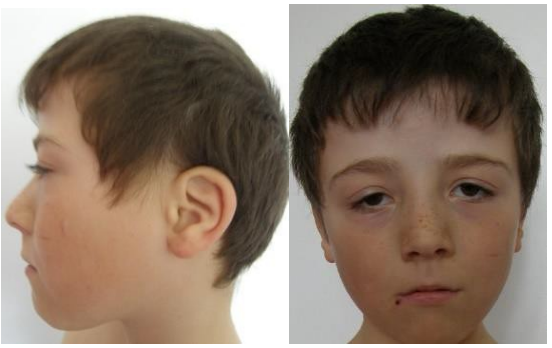


Fig. 4. Facial, hands and feet appearance (sister)

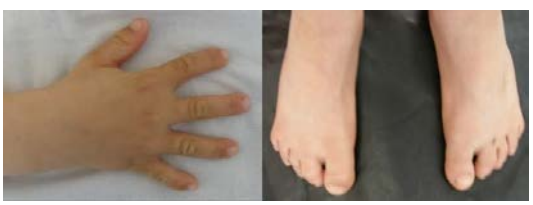


Fig. 5. Facial, hands and feet appearance (brother)

Discussions

Based on the clinical findings, we proceeded with the genetic testing using MS-MLPA (MRC Holland P080 kit) to identify the mutation in the *TWIST1* gene. This way all cases were confirmed molecular with SCS.

In this family clinical finding were quite similar among the affected members, with a varying degree of severity of the phenotypic features. The craniofacial abnormalities seem to fit in the diagnostic criteria: the majority of the patients with SCS have palpebral ptosis, deviated septum, acrocephaly [5, 6, 9, 15]. The hands and feet usually show deformities such as brachydactyly, syndactyly and clinodactyly. The neurological modifications were present with both children having different degrees of intellectual disability associated with behavioral problems, leaving the mother without any kind of similar manifestations. In addition, all 3 members of the family associated severe deafness, probably the conductive type even though in SCS the most common is mild to moderate hearing loss [6, 9, 15]. Associated cardiac and renal defects described in the literature were not found in any of our patients [13, 16, 17].

In this family, the *TWIST1* gene is transmitted in an autosomal dominant trait. The mother presented mild anomalies compared with the children showing this way the phenotypic variability found in SCS but further investigations are necessary to evaluate her properly.

Every case that is diagnosed with SCS needs as well a detailed family history to clarify the genetic status for all family members but the variable phenotypic manifestations of *TWIST1* gene variants complicate often the genetic counseling [14, 16, 17].

Depending on the degree of severity, patients diagnosed require long term care from a multidisciplinary team for the right management and treatment [6, 9, 16, 17].

Often increased intracranial pressure requires cranioplasty in individuals with multiple sutural synostosis in the first year of life [6, 17]. Some associate dental malocclusion, cleft palate, respiratory issues, all of them needing surgical intervention. Periodic ophthalmological evaluation is required if ptosis is present and for other complications associated; hearing loss should be treated in a standard manner with periodical audiological evaluations. Special education is suggested with annual evaluation of the developmental status since some present intellectual disability of various degrees [6, 9, 17].

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